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Research Update E- Newsletter
September – October – November 2021
www.nva.org

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Vulvodynia

Microablative Erbium: YAG Laser Therapy for Vulvodynia - A Report on Efficacy, Safety, and Treatment Satisfaction

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Sex Med. 2021 Sep 19;9(6):100432. doi: 10.1016/j.esxm.2021.100432.
https://pubmed.ncbi.nlm.nih.gov/34551383/

Introduction: Treatment for vulvodynia is challenging and a multidisciplinary approach is recommended. **Aim:** To examine the effectiveness, safety and treatment satisfaction of vulvovaginal microablative laser treatment for vulvodynia. **Methods:** Case study of women who received laser treatment as part of a multidisciplinary treatment program for vulvodynia. Subjective improvement was compared to a retrospective cohort of women treated for vulvodynia without LASER therapy. LASER treatment was offered to women with vulvodynia presenting to a gynecologic pain clinic of a tertiary university hospital. LASER treatments were performed with a microablative 2,940 nm Er:YAG LASER and potentially repeated after 1 month. **Main outcome measures:** Change in local vulvar pain was assessed with cotton-swab tests and rated on a numeric rating scale (NRS). Treatment discomfort and short-term adverse events were recorded. The Freiburg Index of Patient Satisfaction was used to assess treatment satisfaction. Subjective symptom improvement was assessed with the Patient Global Impression of Improvement questionnaire. **Results:** 35 women received at least 1 laser treatment, with overall mild treatment adverse effects (mean pain NRS 2.4 ± 1.9) and good treatment satisfaction (mean total score of 27.6 ±5.1; potential range 8-32). One month after last LASER treatment the pain NRS on vulvar cotton swab test improved from 6.1 ± 2.6 at baseline to 3.1 ± 2.6 ($P < .001$), and 74% of women (n = 26) reported symptom improvement. At 9-12 months follow-up 66% reported ongoing symptom improvement, with no significant difference to the control group of 32 women.
Conclusion: Microablative Er:YAG vulvovaginal LASER therapy appears safe and well accepted among vulvodynia patients, but there was no significant difference in symptom improvement compared to a control group.

High rate of dyspareunia and probable vulvodynia in Ehlers-Danlos syndromes and hypermobility spectrum disorders: An online survey

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Am J Med Genet C Semin Med Genet. 2021 Nov 7. doi: 10.1002/ajmg.c.31939.
https://pubmed.ncbi.nlm.nih.gov/34747110/

Vulvodynia is debilitating vulvar pain accompanied by dyspareunia (pain with sexual intercourse). Ehlers-Danlos syndromes (EDS) and hypermobility spectrum disorders (HSD) may represent a predisposing factor for vulvodynia given a high rate of dyspareunia in these conditions. We conducted an online survey of women with EDS or HSD to assess rates of dyspareunia and estimate rates of vulvodynia, report rates of comorbid conditions common to EDS or HSD and vulvodynia, and examine rates of conditions contributing to dyspareunia in women with EDS or HSD. Women with EDS or HSD (N = 1,146) recruited via social media were 38.2 ± 11.5 years old, primarily White (94.4%), and resided in the United States (78.5%). 63.7% of participants reported dyspareunia and 50% screened positive for vulvodynia. The rate of comorbid conditions common to EDS or HSD and vulvodynia were: irritable bowel syndrome, 6.5%; fibromyalgia, 40.0%; temporomandibular joint dysfunction, 56.4%; migraine, 6.7%; interstitial cystitis, 1.7%; and mast cell activation syndrome, 10.2%. Participants reporting dyspareunia also reported ovarian cysts, fibroids, or abdominal or pelvic scars, 47.5%; endometriosis, 26.5%; and genital lacerations, 19.3%. Women with EDS or HSD may have a higher rate of vulvodynia (50.0%) than women in the U.S. population at large (8%) and should be assessed for dyspareunia and vulvodynia.

Health seeking behaviours and treatments received by Australian women with vulvodynia: A cross-sectional survey

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Aust N Z J Obstet Gynaecol. 2021 Aug 31. doi: 10.1111/ajo.13423.
https://pubmed.ncbi.nlm.nih.gov/34463957/

Background: Vulvodynia is a condition characterised by pain in the vulva lasting more than three months and for which no obvious aetiology can be found. It affects around 8% of women and has significant negative impacts on quality of life. There is a paucity of research on healthcare management pathways and the use of evidence-based treatments in an Australian community setting. **Aims:** To explore which healthcare professionals Australian women with vulvodynia seek treatment from, and which treatments are recommended, provided, or prescribed by these healthcare professionals. **Materials and methods:** A cross-sectional online survey was conducted from May 2019 to August 2019. Women were eligible to participate if they had been diagnosed with vulvodynia by a healthcare professional, were currently living in Australia, and were over 18 years old. **Results:** Fifty respondents meet the inclusion criteria, with a mean age of 30.5 years. On average, respondents reported seeing four different types of healthcare professionals in the management of their vulvodynia, with general practitioners (GPs) (98%), medical specialists (96%), and physiotherapists (80%) being the three most commonly consulted. Most respondents reported seeing multiple GPs (>87%), multiple medical specialists (>77%), and multiple physiotherapists (50%). The most commonly prescribed interventions were pelvic floor down-training exercises (76%), topical (70%) and oral (70%) medication, and vulvodynia information (56%). **Conclusions:** Australian women with vulvodynia seek help from several professionals and receive a variety of treatments for their pain. Of concern is many treatments that are being offered clinically have very little peer-reviewed evidence of effectiveness in vulvodynia.

Care Seeking for Chronic Vulvar Pain Among a Large, Population-Based Sample of Reproductive-Aged Women

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J Womens Health (Larchmt). 2021 Sep 14. doi: 10.1089/ jwh.2021.0086.

https://pubmed.ncbi.nlm.nih.gov/34520267/

Background: Chronic vulvar pain is a prevalent but often misdiagnosed and undertreated condition that adversely impacts quality of life. A large proportion of women report not seeking care for chronic vulvar pain, but little is known about the factors that underlie care-seeking decisions. **Materials and Methods:** We used a large, population-based survey of women aged 18-40 years to assess a history of chronic vulvar burning, pain on contact, or itching that had lasted ≥3 months. The survey also captured demographic characteristics and comorbidities. Women were asked if they had ever sought care for their chronic vulvar condition. Demographic characteristics and comorbidities were evaluated across pain categories and by care-seeking behaviors. **Results:** A higher proportion of women who described their pain as burning only and both burning and pain on contact had sought care for their pain (69.2% and 85.2%, respectively) compared with pain on contact only (41.8%). Women who described their pain as pain on contact only were also less likely to see multiple providers and to have ever received treatment for their pain. Care seekers were more likely to be married, have a college education, have a normal body mass index, and have multiple gynecologic comorbidities. **Conclusions:** Our study suggests that care-seeking behavior varies by pain type. Less than half of women who characterized their pain as pain on contact had sought medical care. Those who did seek care reported seeing fewer providers than those who experienced burning. Providers may wish to proactively ask patients about pain on contact.

Provoked Vestibulodynia

Transcranial direct current stimulation for provoked vestibulodynia: What roles do psychosexual factors play in treatment response?

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J Clin Neurosci. 2021 Nov;93:54-60. doi: 10.1016/j.jocn.2021.08.003. Epub 2021 Sep 11.

https://pubmed.ncbi.nlm.nih.gov/34656261/

There is growing evidence that provoked vestibulodynia (PVD), a frequent and debilitating condition, is characterized by central sensitization. This study aimed to examine predictive factors of transcranial direct current stimulation (tDCS) efficacy in this chronic pain population. Exploratory analysis derived from a randomized controlled trial was performed to assess predictors of pain reduction among 39 women with PVD who received 10 daily sessions of either active or sham tDCS. Clinical characteristics (e.g. pain intensity, duration and pain sensitivity) and psychosexual factors (e.g. pain catastrophizing, pain-related fear, anxiety, depressive symptoms and vaginal penetration cognitions) were assessed at baseline and used to predict tDCS response at 3-month follow-up. Analysis revealed that higher depressive symptoms and lower negative self-image cognitions were significant predictors of pain reduction at follow-up and accounted for 62.3% of the variance in the active tDCS group. Higher genital incompatibility cognitions were related to poorer response, regardless of treatment group. These findings suggest that women with PVD presenting higher depressive symptoms and lower levels of negative self-image cognitions could derive greater benefits from tDCS. These results suggest that tDCS

could be effective in a subgroup of women with PVD - a possibility worth exploring with future prospective larger studies.

Reduced concentrations of vaginal metabolites involved in steroid hormone biosynthesis are associated with increased vulvar vestibular pain and vaginal muscle tenderness in provoked vestibulodynia: An exploratory metabolomics study
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Mol Pain. Jan-Dec 2021;17:17448069211041853. doi: 10.1177/17448069211041853.
https://pubmed.ncbi.nlm.nih.gov/34505814/

Provoked vestibulodynia (PVD) is a chronic vulvar pain disorder characterized by hypersensitivity and severe pain with pressure localized to the vulvar vestibule. Knowledge regarding pathophysiological mechanisms contributing to the etiology and production of symptoms in PVD remains incomplete but is considered multifactorial. Using a cross-sectional observational study design, data from untargeted metabolomic profiling of vaginal fluid and plasma in women with PVD and healthy women was combined with pain testing and brain imaging in women with PVD to test the hypotheses that women with PVD compared to healthy women show differences in vaginal and plasma metabolites involved in steroid hormone biosynthesis. Steroid hormone metabolites showing group differences were correlated with vulvar vestibular pain and vaginal muscle tenderness and functional connectivity of brain regions involved in pain processing in women with PVD to provide insight into the functional mechanisms linked to the identified alterations. Sensitivity analyses were also performed to determine the impact of hormonal contraceptive use on the study findings. Women with PVD compared to healthy controls had significant reductions primarily in vaginal fluid concentrations of androgenic, pregnenolone and progestin metabolites involved in steroidogenesis, suggesting localized rather than systemic effects in vagina and vulvar vestibule. The observed reductions in androgenic metabolite levels showed large effect size associations with increased vulvar vestibular pain and vulvar muscle tenderness and decreases in androgenic and progestin metabolites were associated with decreased connectivity strength in primary sensorimotor cortices. Women with PVD showed symptom-associated reductions in vaginal fluid concentrations of metabolites involved in the biosynthesis of steroid hormones previously shown to affect the integrity of vulvar and vaginal tissue and nociceptive processing. Deficiency of certain steroids may be an important mechanism contributing to the pathophysiology of symptoms in PVD may provide potential diagnostic markers that could lead to new targets for therapeutic intervention.

A mucoadhesive biodissolvable thin film for localized and rapid delivery of lidocaine for the treatment of vestibulodynia
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Int J Pharm. 2021 Nov 17;121288. doi: 10.1016/j.ijpharm.2021.121288.
https://pubmed.ncbi.nlm.nih.gov/34800616/

Vestibulodynia (VBD), an idiopathic pain disorder characterized by erythema and pain of the vulvar vestibule (the inner aspect of the labia minora and vaginal opening), is the most common cause of sexual pain for women of reproductive age. Women also feel discomfort with contact with clothing and tampon use. As most women with this disorder only have pain with provocation of the tissue, topical

anesthetics applied to the vestibule are the current first line treatment for temporary pain relief. Treatment options are limited due to anatomical constraints of the vestibular region, poor drug retention time, imprecise dosing, leakage, and overall product messiness. In this study we report a novel approach to treatment of VBD using thin film designed to fit the vulvar vestibule and deliver lidocaine locally. Two use cases for VBD treatment were identified 1) rapid drug release (<5 min), for use prior to intercourse and 2) long-acting release (≥120 min) for prolonged use and relief throughout the day. Cellulose-based mucoadhesive thin films were fabricated using a solvent casting method. Three polymers including hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), and hydroxypropylmethycellulose (HMPC), were selected owing to their biocompatibility and ideal properties for film casting. Films casted with HEC, HPC, and HPMC exhibited mucoadhesive properties relative to a control, with the highest mucoadhesive force recorded for films casted with HPC. Effect of media volume, pH, presence of mucin and presence of drug on film dissolution rates were investigated. Dissolution rates were independent of media volume, media pH or drug presence, whereas faster dissolution rates were obtained for all films in presence of mucin. In vitro lidocaine release kinetics were influenced by polymer type, percent drug loading and film casting thickness. Lidocaine release was based on a diffusion mechanism rather than through film dissolution and faster release (∼5 min) was observed for HEC films compared HPC films (∼120 min). Higher drug loading and film thickness resulted in slower and more prolonged release kinetics of lidocaine. All films were biocompatible and exhibited good mechanical properties. Two film formulations (9% w/w HPC with 12% w/w LHC, 5% w/w HEC with 6% w/w LHC) were optimized to meet the two use case scenarios for VBD treatment and moved into in vivo testing. In vivo testing demonstrated the safety of the films in BALB/c mice, and the pharmacokinetic analysis demonstrated the delivery of lidocaine primarily to the vaginal tissue. We demonstrate the ability to develop a mucoadhesive, biodissolvable thin film and fine-tune drug release kinetics to optimize local delivery of lidocaine to the vulva.

Predictors and Moderators of Provoked Vestibulodynia Treatment Outcome Following a Randomized Trial Comparing Cognitive-Behavioral Couple Therapy to Overnight Lidocaine

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Behav Ther. 2021 Nov;52(6):1502-1515. doi: 10.1016/j.beth.2021.05.002. Epub 2021 May 13.
https://pubmed.ncbi.nlm.nih.gov/34656202/

Provoked vestibulodynia is a vulvar pain condition causing sexual dysfunction, affecting 8% to 10% of women. Our recently published randomized clinical trial (N = 108 couples) found that cognitive behavioral couple therapy (CBCT) and topical lidocaine reduced women's pain and associated sexual symptoms, with CBCT showing more benefits. Little is known about pretreatment predictors of treatment outcomes in couples sex therapy. In the current study, we examined women and their partners' pretreatment demographic (age, relationship length), clinical (pain duration, anxiety) and interpersonal (partner responses to pain, sexual goals) predictors/moderators of women's pain intensity, pain unpleasantness, and sexual function at posttreatment and 6-month follow-up. Longer relationship duration, lower anxiety in women, partner higher solicitousness and partner higher approach sexual goals predicted better pain outcomes for women with PVD irrespective of treatment condition. CBCT was more effective than lidocaine for improving women's sexual function at posttreatment when, at pretreatment, women had partners with higher anxiety and women reported lower approach sexual goals, whereas lidocaine was more effective for improving women's sexual function at follow-up when partners had higher approach sexual goals. Findings can assist clinicians in determining what treatment will be most beneficial for whom.

Co-morbid Disorders

Low-pressure hydrodistension induces bladder glomerulations in female patients with interstitial cystitis/bladder pain syndrome
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Neurourol Urodyn. 2021 Oct 11. doi: 10.1002/nau.24818.
https://pubmed.ncbi.nlm.nih.gov/34633704/

Aims: The role of hydrodistension in the diagnosis of interstitial cystitis/bladder pain syndrome (IC/BPS) is controversial. This study evaluated the effect of low-pressure hydrodistension on glomerulation formation in female patients diagnosed with the disease. **Methods:** Sixty female patients with the clinical diagnosis of IC/BPS and 30 female controls without the disease underwent cystoscopy and hydrodistension. Cold-cup biopsy was taken from bladder posterior wall at sites with normal cystoscopic appearance before hydrodistension in the IC/BPS group. The tissue samples were processed for histology study. Low-pressure (40 cmH_2O) hydrodistension for 2 min was performed and the appearance of glomerulations was compared between the two groups. High-pressure (80 cmH_2O) hydrodistension for 8 min was then performed as a therapeutic measure for the IC/BPS patients. Further changes to the degree of glomerulations were recorded. **Results:** Histology showed pathological changes in the normal-appearing IC/BPS bladder mucosa including urothelium denudation, inflammatory cell infiltration, stromal edema, fibrosis, and vascular congestion. Low-pressure hydrodistension induced significant glomerulation formation in the patient group (percentage of patients with Grades 0-4: 0%, 8.3%, 40%, 35%, 10%, respectively) while none in the controls. High-pressure hydrodistension further increased the glomerulation grading in the IC/BPS patients. **Conclusions:** Structural changes are present in prehydrodistension IC/BPS bladder wall, which may not be macroscopically detectable. Hydrodistension at low pressure is adequate to disrupt the integrity of such diseased mucosa and offers a more discriminative test in the diagnosis of IC/BPS.

Gluten-free Diet Reduces the Risk of Irritable Bowel Syndrome: A Mendelian Randomization Analysis
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Front Genet. 2021 Nov 9;12:684535.doi: 10.3389/fgene.2021.684535. eCollection 2021.
https://pubmed.ncbi.nlm.nih.gov/34899821/

Background: Whether a gluten-free diet (GFD) is a cause of irritable bowel syndrome (IBS) remains controversial. We aim at exploring the causal relationship between gluten intake and IBS within Mendelian randomization (MR) design. **Methods:** We conducted a two-sample MR and selected single-nucleotide polymorphisms (SNPs) associated with GFD as instrumental variables (IVs). SNPs and genetic associations with GFD and IBS were obtained from the latest genome-wide association studies (GWAS) in Europeans (GFD: cases: 1,376; controls: 63,573; IBS: cases:1,121; controls: 360,073). We performed inverse variance weighting (IVW) as the primary method with several sensitivity analyses like MR-Egger and MR-PRESSO for quality control. The above analyses were re-run using another large dataset of IBS, as well as changing the *p*-value threshold when screening IVs, to verify the stability of the results. **Results:** The final estimate indicated significant causal association [per one copy of effect allele predicted log odds ratio (OR) change in GFD intake: OR = 0.97, 95% confidence interval (CI) 0.96 to 0.99, $p < 0.01$] without heterogeneity statistically (Q = 2.48, $p = 0.78$) nor horizontal pleiotropy biasing the causality ($p = 0.92$). Consistent results were found in validation analyses. Results of MR Steiger directionality test indicated the accuracy of our estimate of the causal direction (Steiger $p <$

0.001). **Conclusion:** GFD might be a protective factor of IBS. Therefore, we suggest taking a diet of lower gluten intake into account in IBS prevention and clinical practice.

EEG-heart rate connectivity changes after sensorimotor rhythm neurofeedback training: Ancillary study

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Neurophysiol Clin. 2021 Dec 11;S0987-7053(21)00124-6. doi: 10.1016/j.neucli.2021.11.003.
https://pubmed.ncbi.nlm.nih.gov/34906429/

Objectives: Neurofeedback can induce long-term changes in brain functional connectivity, but its influence on the connectivity between different physiological systems is unknown. The present paper is an ancillary study of a previous paper that confirmed the effect of neurofeedback on brain connectivity associated with chronic pain. We analysed the influence of neurofeedback on the connectivity between the electroencephalograph (EEG) and heart rate (HR). **Methods:** Seventeen patients diagnosed with fibromyalgia were divided into three groups: good sensorimotor rhythm (SMR) training responders (n = 4), bad SMR responders (n = 5) and fake training (SHAM, n = 8). Training consisted of six sessions in which participants learned to synchronize and desynchronize SMR power. Before the first training (pre-resting state) and sixth training (post-resting state) session, open-eye resting-state EEG and electrocardiograph signals were recorded. **Results:** Good responders reduced pain ratings after SMR neurofeedback training. This improvement in fibromyalgia symptoms was associated with a reduction of the connectivity between the central area and HR, between central and frontal areas, within the central area itself, and between central and occipital areas. The sham group and poor responders experienced no changes in their fibromyalgia symptoms. **Conclusions:** Our results provide new evidence that neurofeedback is a promising tool that can be used to treat of chronic pain syndromes and to obtain a better understanding of the interactions between physiological networks. These findings are preliminary, but they may pave the way for future studies that are more methodologically robust. In addition, new research questions are raised: what is the role of the central-peripheral network in chronic pain and what is the effect of neurofeedback on this network.

Treatment with low-intensity transcranial magnetic stimulation in women with fibromyalgia improves diagnostic variables up to 6 months after treatment completion

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Clin Exp Rheumatol. 2021 Nov 29.
https://pubmed.ncbi.nlm.nih.gov/34905482/

Objectives: Fibromyalgia (FM) is a disease treated with various therapeutic approaches that have limited success. Pulsed electromagnetic field therapy has been proposed as a possible solution to reduce several symptoms. This study aims to analyse the therapeutic effects of transcranial low-intensity magnetic stimulation (LIMS) in women diagnosed with FM at 2, 12 and 24 weeks from the last LIMS administration treatment session. **Methods:** 560 women (53.7 ± 11.3 years) diagnosed with FM according to the ACR 2016 criteria were randomly allocated in two groups: 280 received standard pharmacological treatment and 280 received the same treatment plus eight sessions of LIMS, 20 minutes long, once a week. The variables analysed were the widespread pain index (WPI), symptoms severity score (SS score) and the Spanish-validated version of the FM impact questionnaire (S-FIQ). The evaluations were performed at the beginning of LIMS treatment and at 2, 12 and 24 weeks after the end of the last LIMS treatment session. **Results:** From the second week after the last LIMS session, there was

significant improvement (p <0.001) in the variables WPI, SS score and S-FIQ. This improvement was maintained throughout the 24 weeks of monitoring after the last intervention. The age of the patients and the severity of the symptoms at the time of diagnosis did not affect the improvement observed in the three variables studied. **Conclusions:** Treatment with LIMS for eight weeks resulted in significant improvement in FM diagnostic variables, which was maintained up to 24 weeks after the last treatment session. This therapy could be recommended as a part of a multimodal approach for FM treatment.

Neuromuscular treatment approach for women with chronic pelvic pain syndrome improving pelvic pain and functionality

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Neurourol Urodyn. 2021 Sep 16. doi: 10.1002/nau.24799.

https://pubmed.ncbi.nlm.nih.gov/34529875/

Aims: Reporting the effects of treating underlying myofascial dysfunction and neuropathic pain in women with chronic pelvic pain syndrome (CPPS). **Methods:** Retrospective longitudinal study of 186 women with CPPS treated with ultrasound-guided peripheral nerve blocks and trigger point injections to pelvic floor muscles alongside pelvic floor physical therapy once weekly for 6 weeks in an outpatient setting. Visual Analogue Scale (VAS) and Functional Pelvic Pain Scale (FPPS) questionnaires quantified pain and function in the pelvis. Working, intercourse, sleeping, walking, running, lifting, bladder, and bowel were the function categories. Statistical significance was established by p value less than .05 in paired two-sample t-test. **Results:** VAS improved by 2.14 where average VAS before treatment was 6.61 (standard deviation [SD] 2.45; $p < .05$, 95% confidence interval [CI] = 6.26-6.96) and average VAS after treatment was 4.47 (SD 2.71; $p < .05$, 95% CI = 4.08-4.86). Total FPPS decreased by 3.38 from 11.26 (SD 6.51; $p < .05$, 95% CI = 10.32-12.19) before treatment to 7.88 (SD 6.22; $p < .05$, 95% CI = 6.99-8.78) after treatment. Working, intercourse, and sleeping accounted for the highest statistically significant improvement. **Conclusion:** Findings support the success of the comprehensive treatment protocol. Patients who had persistent symptoms after a full course of pelvic floor physical therapy experienced improvements in pain levels and function once it was combined with ultrasound-guided nerve blocks and trigger point injections, interactively treating underlying neuromuscular dysfunction.

Use of Intravesical Injections of Platelet-Rich Plasma for the Treatment of Bladder Pain Syndrome: A Comprehensive Literature Review

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Antibiotics (Basel). 2021 Oct 1;10(10):1194. doi: 10.3390/antibiotics10101194.

https://pubmed.ncbi.nlm.nih.gov/34680774/

Background: Bladder pain syndrome/interstitial cystitis (BPS/IC) or primary bladder pain syndrome (PBPS) is a complex and poorly understood condition. This comprehensive review aimed to discuss the potential application of platelet-rich plasma (PRP) in the treatment of BPS/IC. The pathophysiology of BPS/IC is characterized by urothelial damage that triggers a chain of events leading to chronic inflammation and other conditions. Frequently, in subjects affected by BPS/IC, recurrent urinary tract infection (rUTI) is associated with difficult therapeutic management. For these reasons, many oral and intravesical treatments (e.g., antibiotic therapy and intravesical anesthetic instillations) have been proposed to alleviate the symptoms of IC/BPS. However, the limitation of these treatments is the short

duration of improvement. The purpose of this review is to analyze the efficacy of intravesical PRP injections in subjects with PBS/IC and to try to understand the potential therapeutic effects on the pathophysiology of this disease. **Methods:** A nonsystematic literature search using Pubmed, EMBASE, Scopus, Web of Science, Medline was performed from January 2000 to August 2021. The following terms were combined to capture relevant publications: "platelet-rich plasma", "interstitial cystitis", "PRP", "bladder pain syndrome", and "painful bladder syndrome". **Results:** After exclusion of non-pertinent studies/articles, we have analyzed 5 studies. In detail, 2 articles concerned preclinical studies in which animal models were used. The authors showed an improvement in the histological pattern with less bleeding in treated subjects, a lower presence of inflammatory cytokines and an increase in the mitotic index of urothelial cells in animals treated with intravesical PRP. In the three prospective clinical trials analyzed, patients with BPS/IC who underwent monthly intravesical PRP injections were found to have a statistically significant improvement in symptoms with modulation of growth factors and inflammatory proteins. **Conclusions:** New evidence suggests that treatment with intravesical PRP could improve urothelial regeneration and reduces chronic inflammation in BPS/IC, modifying the clinical history of its pathology.

Possible role of intravenous administration of mesenchymal stem cells to alleviate interstitial cystitis/bladder pain syndrome in a Toll-like receptor-7 agonist-induced experimental animal model in rat

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BMC Urol. 2021 Nov 13;21(1):156. doi: 10.1186/s12894-021-00923-3.

https://pubmed.ncbi.nlm.nih.gov/34774029/

Background: Interstitial cystitis/bladder pain syndrome (IC/BPS) categorized with and without Hunner lesions is a condition that displays chronic pelvic pain related to the bladder with no efficacious treatment options. There are strong associations suggested between Hunner-type IC and autoimmune diseases. Recently, we established an animal model of Hunner-type IC using a Toll-like receptor-7 (TLR7) agonist. Intravenous infusion of mesenchymal stem cells (MSCs) can be used to treat injury via multimodal and orchestrated therapeutic mechanisms including anti-inflammatory effects. Here, we investigated whether infused MSCs elicit therapeutic efficacy associated with the TLR7-related anti-inflammatory pathway in our Hunner-type IC model. **Methods:** Voiding behaviors were monitored 24 h prior to the Loxoribine (LX), which is a TLR7 agonist instillation in order to establish a Hunner-type IC model (from - 24 to 0 h) in female Sprague-Dawley rats. LX was instilled transurethrally into the bladder. At 0 h, the initial freezing behavior test confirmed that no freezing behavior was observed in any of the animals. The LX-instilled animals were randomized. Randomized LX-instilled rats were intravenously infused with MSCs or with vehicle through the right external jugular vein. Sampling tissue for green fluorescent protein (GFP)-positive MSCs were carried out at 48 h. Second voiding behavior tests were monitored from 72 to 96 h. After the final evaluation of the freezing behavior test at 96 h after LX instillation (72 h after MSC or vehicle infusion), histological evaluation with H&E staining and quantitative real-time polymerase chain reaction (RT-PCR) to analyze the mRNA expression levels of inflammatory cytokines were performed. **Results:** Freezing behavior was reduced in the MSC group, and voiding behavior in the MSC group did not deteriorate. Hematoxylin-eosin staining showed that mucosal edema, leukocyte infiltration, and hemorrhage were suppressed in the MSC group. The relative expression of interferon-β mRNA in the bladder of the MSC group was inhibited. Numerous GFP-positive MSCs were distributed mainly in the submucosal and mucosal layers of the inflammatory bladder wall.

Conclusion: Intravenous infusion of MSCs may have therapeutic efficacy in a LX-instilled Hunner-type IC rat model via a TLR7-related anti-inflammatory pathway.

[Endometriosis and chronic overlapping pain conditions]
[Article in German]
Winfried Häuser
Schmerz. 2021 Jun;35(3):179-182. doi: 10.1007/s00482-021-00535-8. Epub 2021 Feb 11.
https://pubmed.ncbi.nlm.nih.gov/33576864/

Background: The concept of chronic overlapping pain conditions (COPC) is relatively unknown in German pain medicine. **Aims:** Definition, prevalence, shared etiological and pathophysiological mechanisms of COPC. Summary of recommendations of the interdisciplinary S2k guidelines on diagnostics and treatment of endometriosis relevant for pain physicians. **Methods:** Selective search of literature in PubMed and selection of recommendations of the S2k guidelines on diagnostics and treatment of endometriosis. **Results:** According to the US National Institutes of Health, COPCs comprise chronic fatigue syndrome, chronic (unspecific) low back pain, chronic tension headache, endometriosis, fibromyalgia syndrome, migraine, painful bladder syndrome, temporomandibular disorder and vulvodynia. Shared etiological factors are family aggregation, childhood adversities and major or traumatic life events. A major shared pathophysiological mechanism is altered processing of stimuli in the central nervous system. Patients with endometriosis should be screened for other chronic pain conditions and psychological distress. The physical examination should check for local (myofascial trigger points) and generalized signs of hyperalgesia and allodynia indicating central sensitization. In cases of endometriosis with COPCs repeated surgery for pain relief should be avoided. Amitriptyline and duloxetine can be considered as pharmacological treatment options. **Discussion:** Pain physicians can play a role in the management of patients with endometriosis and COPCs. A multimodal therapy should include physiotherapy and pain-related psychological treatment and possibly centrally acting pain modulation medication.

Motivational Determinants of Objective Physical Activity in Women with Fibromyalgia Who Attended Rehabilitation Settings
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J Clin Med. 2021 Nov 26;10(23):5547. doi: 10.3390/jcm10235547.
https://pubmed.ncbi.nlm.nih.gov/34884246/

Being physically active has positive effects on fibromyalgia functioning. However, promoting an active lifestyle in these patients continues to be a relevant clinical challenge. Our aim was to test a motivational model to explain light (LPA) and moderate-vigorous physical activity (MVPA). A cross-sectional prospective study was conducted at a tertiary level of care. Participants completed sociodemographic, clinical, motivational (physical activity self-efficacy and goal preferences) and behavioral measures (activity avoidance). LPA and MVPA were measured with triaxial accelerometers, starting the same day of the aforementioned assessment. Out of 211 women, 183 completed this measure. Structural models were performed. Our results show that the best fit indices (CFI = 0.97, SRMR = 0.04) showed a model with direct influence of PA self-efficacy on MVPA ($p < 0.01$) and indirect influence on LPA ($p < 0.001$). LPA received the influence of PA self-efficacy mainly through activity avoidance ($p < 0.01$). Clinical variables did not have any effect on PA intensities. Thus, the motivational

variables showed different paths to explain two PA intensities. Targeting PA self-efficacy in rehabilitation settings is needed to enhance both daily LPA and MVPA intensities.

COVID-19 as a trigger of irritable bowel syndrome: A review of potential mechanisms
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World J Gastroenterol. 2021 Nov 21;27(43):7433-7445. doi: 10.3748/wjg.v27.i43.7433.
https://pubmed.ncbi.nlm.nih.gov/34887641/

In December 2019 a novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), started spreading from Wuhan city of Chinese Hubei province and rapidly became a global pandemic. Clinical symptoms of the disease range from paucisymptomatic disease to a much more severe disease. Typical symptoms of the initial phase include fever and cough, with possible progression to acute respiratory distress syndrome. Gastrointestinal manifestations such as diarrhoea, vomiting and abdominal pain are reported in a considerable number of affected individuals and may be due to the SARS-CoV-2 tropism for the peptidase angiotensin receptor 2. The intestinal homeostasis and microenvironment appear to play a major role in the pathogenesis of COVID-19 and in the enhancement of the systemic inflammatory responses. Long-term consequences of COVID-19 include respiratory disturbances and other disabling manifestations, such as fatigue and psychological impairment. To date, there is a paucity of data on the gastrointestinal sequelae of SARS-CoV-2 infection. Since COVID-19 can directly or indirectly affect the gut physiology in different ways, it is plausible that functional bowel diseases may occur after the recovery because of potential pathophysiological alterations (dysbiosis, disruption of the intestinal barrier, mucosal microinflammation, post-infectious states, immune dysregulation and psychological stress). In this review we speculate that COVID-19 can trigger irritable bowel syndrome and we discuss the potential mechanisms.

Managing Female Sexual Pain
Maria Uloko, Rachel Rubin
Urol Clin North Am . 2021 Nov;48(4):487-497. doi: 10.1016/j.ucl.2021.06.007.
https://pubmed.ncbi.nlm.nih.gov/34602170/

Female sexual pain disorder or genito-pelvic pain/penetration disorder (GPPPD), previously known as dyspareunia, is defined as persistent or recurrent symptoms with one or more of the following for at least 6 months: marked vulvovaginal or pelvic pain during penetrative intercourse or penetration attempts, marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during, or as a result of penetration, and marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration. In this review, we discuss etiology, diagnosis, and treatment for common disorders that cause GPPD.

"The Urinary Proteomic Profile Implicates Key Regulators for Urologic Chronic Pelvic Pain Syndrome (UCPPS): A MAPP Research Network Study"

John W Froehlich, Hsin-Hsaio Scott Wang, Tanya Logvinenko, Stephen Kostel, Shannon DiMartino, Adrie van Bokhoven, Marsha A Moses, Richard S Lee, MAPP Research Network

Mol Cell Proteomics . 2021 Nov 10;100176. doi: 10.1016/j.mcpro.2021.100176.
https://pubmed.ncbi.nlm.nih.gov/34774759/

Urologic chronic pelvic pain syndrome (UCPPS) is a condition of unknown etiology characterized by pelvic pain, and urinary frequency and/or urgency. As the proximal fluid of this syndrome, urine is an ideal candidate sample matrix for an unbiased study of UCPPS. In this study, a large, discovery-phase, TMT-based quantitative urinary proteomics analysis of 244 subjects was performed. The subjects included patients with UCPPS (n=82), healthy controls (HC) (n=94) and disparate chronic pain diseases, termed positive controls (PC) (n=68). Utilizing training and testing cohorts, we identified and validated a small and distinct set of proteins that distinguished UCPPS from HC (n=9) and UCPPS from PC (n=3). Validated UCPPS: HC proteins were predominantly ECM/ECM modifying or immunomodulatory/host defense in nature. Significantly varying proteins in the UCPPS: HC comparison were overrepresented by members of several dysregulated biological processes including decreased immune cell migration, decreased development of epithelial tissue and increased bleeding. Comparison with the PC cohort enabled evaluation of UCPPS-specific upstream regulators, contrasting UCPPS with other conditions that cause chronic pain. Specific to UCPPS were alterations in the predicted signaling of several upstream regulators, including alpha-catenin, IL6, EGF, and TGFB1, among others. These findings advance our knowledge of the etiology of UCPPS and inform potential future clinical translation into a diagnostic panel for UCPPS.

Vulvar Crohn's Disease: Clinical Features and Outcomes

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Am J Gastroenterol. 2021 Nov 1;116(11):2296-2299. doi: 10.14309/ajg.0000000000001502.
https://pubmed.ncbi.nlm.nih.gov/34732676/

Introduction: Vulvar involvement is a rare complication of Crohn's disease (CD). The optimal treatment of vulvar CD is unknown. **Methods:** We conducted a 25-year retrospective cohort study of vulvar CD from 3 referral centers. Clinical features and outcomes were studied. **Results:** Fifty patients were identified. The most common vulvar symptoms were pain (74%), edema (60%), ulcerations (46%), nodules (36%), and abscess (34%). Medical management leading to symptomatic improvement varied, and 5 patients ultimately required surgery. **Discussion:** Vulvar CD manifests with a broad spectrum of symptoms. Aggressive medical management was frequently effective, although surgery was required in 10% of cases.

Anococcygeal Nerve and Sitting Pain: Differential Diagnosis and Treatment Results

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Ann Plast Surg. 2021 Oct 7. doi: 10.1097/SAP.0000000000002920.
https://pubmed.ncbi.nlm.nih.gov/34670963/

Background: The plastic surgeon is often asked to reconstruct the sacral area related to pilonidal cysts or a tumor, or after other surgery, such as coccygectomy. When sitting pain is not due to the pudendal or posterior femoral cutaneous nerve injury, the anococcygeal nerve (ACN) must be considered. Clinically, its anatomy is not well known. Rather than consider coccygectomy when the traditional nonoperative treatment of coccydynia fails, resection of the ACN might be considered. **Methods:** A review of traditional anatomy textbooks was used to establish classical thoughts about the ACN. A retrospective cohort of patients with sitting pain related to the coccyx was examined, and those operated on, by resecting the ACN, were examined for clinicopathologic correlations. **Results:** When the ACN is described in anatomy textbooks, it is with varying distributions of innervated skin territory and nerve root composition. Most include an origin from sacral 5 and coccygeal 1 ventral roots. Most agree that the ACN forms on the ventral side of the sacrum/coccyx, alongside the coccygeus muscle, to emerge laterally and travel dorsally to innervate skin over the coccyx and lower sacrum. A review of 13 patients with sitting pain due to the ACN, from 2015 to 2019, demonstrated a mean age of 54.6 years. Eleven were female. The etiologies of ACN injury were falls (9), exercise (3), and complication from surgery (1). Six of the 9 patients who had surgery were able to be followed up with a mean length of 36.3 months (range, 11-63 months). Overall, 3 had an excellent result, 2 had a good result, and 1 was not improved. The one with a failed result showed improvement with coccygectomy. **Conclusions:** The ACN must be included in the differential diagnosis of sitting pain. It is most often injured by a fall. The ACN can be evaluated with a diagnostic nerve block, can be identified at surgery, and can be resected, and its proximal end can be implanted into the coccygeus muscle. This surgery may prove an alternative to coccygectomy.

Persistent Genital Arousal Disorder

Diagnostic criteria for enduring sexual dysfunction after treatment with antidepressants, finasteride and isotretinoin

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Int J Risk Saf Med. 2021 Oct 26. doi: 10.3233/JRS-210023.
https://pubmed.ncbi.nlm.nih.gov/34719438/

Background: A set of enduring conditions have been reported in the literature involving persistent sexual dysfunction after discontinuation of serotonin reuptake inhibiting antidepressants, 5 alpha-reductase inhibitors and isotretinoin. **Objective:** To develop diagnostic criteria for post-SSRI sexual dysfunction (PSSD), persistent genital arousal disorder (PGAD) following serotonin reuptake inhibitors, post-finasteride syndrome (PFS) and post-retinoid sexual dysfunction (PRSD). **Methods:** The original draft was designed using data from two published case series (Hogan et al., 2014 and Healy et al., 2018), which represent the largest public collections of data on these enduring conditions. It was further developed with the involvement of a multidisciplinary panel of experts. **Results:** A set of criteria were agreed upon for each of the above conditions. Features of PSSD, PFS and PRSD commonly include decreased genital and orgasmic sensation, decreased sexual desire and erectile dysfunction. Ancillary

non-sexual symptoms vary depending on the specific condition but can include emotional blunting and cognitive impairment. PGAD presents with an almost mirror image of unwanted sensations of genital arousal or irritability in the absence of sexual desire. A new term, post-SSRI asexuality, is introduced to describe a dampening of sexual interest and pleasure resulting from a pre-natal or pre-teen exposure to a serotonin reuptake inhibitor. **Conclusions:** These criteria will help in both clinical and research settings. As with all criteria, they will likely need modification in the light of developments.

Persistent Genital Arousal Disorder After Motor Vehicle Accident: A Case Report
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Womens Health Rep (New Rochelle). 2020 Sep 9;1(1):341-344. doi: 10.1089/whr.2020.0043. eCollection 2020.
https://pubmed.ncbi.nlm.nih.gov/33786498/

Persistent genital arousal disorder (PGAD) is a clinical syndrome characterized by persistent unwanted feelings of sexual arousal that are not associated with any specific sexual arousal or stimulus. The severity of symptoms range from mild to severe distress that interrupts daily life for patients. We present a 44-year-old previously healthy woman who developed PGAD after involvement in a motor vehicle accident in 2018. After sustaining lower spinal trauma, 3 months later, she began to experience intermittent tingling feelings in her clitoris. She noticed that exacerbations in back pain were also associated with PGAD symptoms. These symptoms progressively worsened to which she was constantly feeling as if she was on the verge of an orgasm. Her quality of life was severely diminished for 3 months, after which she presented to gynecology. Treatment of lidocaine patches applied to the sacrum were found to completely eliminate the feelings of clitoral stimulation. She also began physical therapy for the residual back pain. One year after initiation of treatment, she has experienced significant improvement in both the back pain and PGAD symptoms. Her quality of life is much improved and plans on continuing a treatment plan of lidocaine patches and physical therapy. Recognition of PGAD in women is important for clinicians as that it can go undiagnosed for long periods of time and can interfere with quality of life for patients.

Pudendal Neuralgia

Recommendations on the management of pudendal nerve entrapment syndrome: A formalised expert consensus
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Eur J Pain. 2021 Oct 13.doi: 10.1002/ejp.1861.
https://pubmed.ncbi.nlm.nih.gov/34643963/

Background: Since the development and publication of diagnostic criteria for pudendal nerve entrapment (PNE) syndrome in 2008, no comprehensive work has been published on the clinical knowledge in the management of this condition. The aim of this work was to develop recommendations on the diagnosis and the management of PNE. **Methods:** The methodology of this study was based on

French High Authority for Health Method for the development of good practice and the literature review was based on the PRISMA method. The selected articles have all been evaluated according to the American Society of Interventional Pain Physicians assessment grid. **Results:** The results of the literature review and expert consensus are incorporated into 10 sections to describe diagnosis and management of PNE: (1) diagnosis of PNE, (2) patients advice and precautions, (3) drugs treatments, (4) physiotherapy, (5) transcutaneous electrostimulations (TENS), (6) psychotherapy, (7) injections, (8) surgery, (9) pulsed radiofrequency, and (10) Neuromodulation. The following major points should be noted: (i) the relevance of 4+1 Nantes criteria for diagnosis; (ii) the preference for initial monotherapy with tri-tetracyclics or gabapentinoids; (iii) the lack of effect of opiates, (iv) the likely relevance (pending more controlled studies) of physiotherapy, TENS and cognitive behavioural therapy; (v) the incertitudes (lack of data) regarding corticoid injections, (vi) surgery is a long term effective treatment and (vii) radiofrequency needs a longer follow-up to be currently proposed in this indication. **Conclusion:** These recommendations should allow rational and homogeneous management of patients suffering from PNE. They should also allow to shorten the delays of management by directing the primary care. **Significance:** Pudendal nerve entrapment (PNE) has only been known for about 20 years and its management is heterogeneous from one practitioner to another. This work offers a synthesis of the literature and international experts' opinions on the diagnosis and management of PNE.

Advances in the therapeutic approach of pudendal neuralgia: a systematic review
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J Osteopath Med. 2021 Nov 22. doi: 10.1515/jom-2021-0119.
https://pubmed.ncbi.nlm.nih.gov/34800013/

Context: Although pudendal neuralgia (PN) has received growing interest over the last few years, diagnosis remains difficult, and many different therapeutic approaches can be considered. **Objectives:** This article aims to provide an overview of the possible treatments of PN and investigate their efficacies. **Methods:** Utilizing PubMed and ScienceDirect databases, a systematic review was carried out and allowed identification of studies involving patients with PN, as defined by Nantes criteria, and their associated treatments. Relevant data were manually reported. **Results:** Twenty-eight articles were selected, totaling 1,013 patients (mean age, 49 years) and six different types of interventions. Clinical outcomes, most frequently quantified utilizing the Visual Analog Scale (VAS), vary greatly with both the therapy and time after intervention (from 100 to <10%). However, neither peri nor postoperative serious complications (grade > II of Clavien-Dindo classification) are reported. Although surgery seems to provide a higher proportion of long-term benefits, identifying the most efficient therapeutic approach is made impossible by the multitude of outcome measurements and follow-up frequencies. It should also be noted that literature is sparse regarding randomized controlled trials with long-term follow-up. **Conclusions:** Although there are a number of modalities utilized for the treatment of PN, there are no current recommendations based on treatment efficacies. This seems to be largely in part caused by the lack of standardization in outcome quantification. Future research in this field should focus on prospective cohort studies with high levels of evidence, aimed at assessing the long-term, if not permanent, benefits of available therapies.

Anatomy, Abdomen and Pelvis, Pudendal Nerve
Kevin J. Kinter, Bruce W. Newton
In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan.
2021 Sep 13.
https://pubmed.ncbi.nlm.nih.gov/32134612/

The pudendal nerve carries motor and sensory axons arising from the ventral rami of the sacral spinal nerves S2-S4. The nerve is paired, meaning that it is found bilaterally, one on the left and one on the right side of the body. The left and right pudendal nerves give off branches, innervating regions of the rectal canal, anus, perineum, and external genitalia. Interestingly, due to the regions it innervates, the nerve's name is originally derived from the Latin word "pudendum." The nerve is important for carrying sensations from the clitoris and penis, labia minora, vaginal vestibule and the lower one-fifth of the vaginal canal, and the posterior aspects of the labia majora and scrotum. It is involved in controlling somatic muscles involved in penile and clitoral erection and in ejaculation in males. Additionally, this nerve innervates the external anal and external urethral sphincters. Based on its location, the nerve can be susceptible to injury, most notably during childbirth. Pudendal nerve injuries can result in loss of sensation in the nerve's distribution, fecal and urinary incontinence, and sexual dysfunction.

Dermatological Conditions

Fractional CO_2 laser treatment as adjunctive therapy to topical steroids for managing vulvar lichen sclerosus
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Lasers Surg Med. 2021 Sep 20. doi: 10.1002/lsm.23476.
https://pubmed.ncbi.nlm.nih.gov/34541702/

Objectives: Uncontrolled vulvar lichen sclerosus (VLS) is often associated with distressful symptoms of genital itch, irritation, and pain and can lead to a pathological process including anatomical changes, scarring, and an elevated risk of cancer in the genital area. First-line topical corticosteroid as monotherapy is frequently not adequate to fully suppress disease activity and control symptoms. This study evaluated the efficacy of fractional CO_2 laser treatments as adjunctive therapy where recalcitrant VLS had been improved, but not adequately controlled, with topical corticosteroid treatment. Outcomes were evaluated up to 12 months after a series of CO_2 laser treatments delivered via a fractional handpiece. **Materials and methods:** Women with a diagnosis of VLS supported by histologic findings on biopsy and/or clinical signs on physical examination received up to five monthly laser treatments. Subjects maintained existing topical corticosteroid and any exogenous hormone treatment during the study. Investigators assessed severity (0 = not present, 1 = mild, 2 = moderate, or 3 = severe) of clinical signs and architectural changes present before adjunctive study interventions and at follow-up visits. Subjects reported the presence of clinical symptoms and impact on quality of life on 4- or 5-point Likert scales. The validated Female Sexual Function Index (FSFI) was used to assess changes in sexual function. Four subjects were biopsied before adjunctive laser treatment and at follow-up. **Results:** Twelve females, 11 postmenopausal, with a mean age of 57 ± 10 years received three to five monthly CO_2 laser treatments. Significant improvement in all prominent clinical signs and architectural changes were reported at the 3- and 6-month follow-ups after the treatment series. Significant improvement was maintained at the 12-month follow-up, with 89% of subjects showing at least one-point improvement in elasticity compared to baseline; 86% in lichenification; 88% in sclerosis; and 80% in whitening and

parchment-like skin. Labial fusion and the extent of disease improved in 50% of patients. Ulcerations present in three subjects at baseline resolved after treatment. Subjects reported 86% improvement in dyspareunia and 83% in skin tearing. Quality of life improved significantly after treatment ($p < 0.01$). The 6-month follow-up FSFI showed significant improvement in sexual function compared to baseline ($p < 0.05$), with a mean point improvement of 4.5. Histology findings after treatment showed some positive improvement, as a decrease in dermal hyalinized zone thickness. There were no treatment complications or adverse events related to the treatment. **Conclusions:** Fractional CO_2 laser treatment outcomes showed improvement in predominant clinical signs and architectural changes in VLS recalcitrant to topical corticosteroid treatment. Adjunctive laser treatment relieved symptoms and improved quality of life as well as sexual function. Fractional CO_2 laser treatment may provide an advanced treatment modality for the management of recalcitrant VLS with improved patient care and sustainable outcomes. Further study in a larger population and with CO_2 laser treatment to both vulvar tissue and the vaginal canal should be explored.

Does compliance to topical corticosteroid therapy reduce the risk of development of permanent vulvar structural abnormalities in pediatric vulvar lichen sclerosus? A retrospective cohort study
Ashod Kherlopian, Gayle Fischer
Pediatr Dermatol . 2021 Nov 4. doi: 10.1111/pde.14840.
https://pubmed.ncbi.nlm.nih.gov/34738263/

Background: Vulvar lichen sclerosus (VLS) is a chronic inflammatory dermatosis of the genital skin, with up to 20% of cases in the pediatric age group. Limited data exist concerning the prognosis of pediatric VLS, particularly the likelihood of permanent architectural change and whether this can be prevented by compliance with topical corticosteroid treatment (TCS). **Objective:** To evaluate the extent to which compliance to TCS treatment influences the risk of developing vulvar structural abnormalities, including clitoral phimosis and diminutive or fused labia minora. **Methods:** A retrospective chart review of case records of pediatric-age females with VLS between January 31, 2004 and January 31, 2021. **Results:** One hundred eighteen cases of VLS were identified, with a mean age at diagnosis of 7.25 years and a mean follow-up period of 42.7 months. Thirty-four girls were "partially compliant," whereas 84 were "compliant." The risk ratio (RR) of developing any vulvar structural abnormality or clitoral phimosis was 5.76 (95% CI 2.96-11.3) and 21.2 (95%CI 5.23-85.9) times higher, respectively, in partially compliant compared with compliant subjects. The RR of a partially compliant female with pre-pubertal onset VLS having a vulvar structural abnormality persisting beyond menarche was increased 3.54-fold relative to compliant females (95% CI 1.75-7.17). **Limitations:** The retrospective nature of our data, lack of a control group, wide variability in follow-up duration, and nonstandardized method of stratifying compliance. **Conclusion:** Vulvar structural abnormalities are common in prepubertal onset VLS. Compliance to TCS appears to be critical in the prognosis of pediatric VLS although attitudes underpinning noncompliance to TCS treatment require further elucidation.

Retrospective analysis of the clinical characteristics and patient-reported outcomes in vulval lichen planus: Results from a single-center study
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J Dermatol. 2021 Oct 19. doi: 10.1111/1346-8138.16191.
https://pubmed.ncbi.nlm.nih.gov/34668211/

Vulval lichen planus (VLP) is a rare, but often chronic, inflammatory disease whose symptoms include genital pain, discomfort, and dyspareunia. The clinical manifestations include erythema, erosions, and scarring. The aim of this study was to longitudinally investigate patient-reported outcomes and clinical findings in patients with VLP. Patients (>18 years) with histologically confirmed VLP were included in the retrospective analysis. Patient demographics, clinical features, symptomatology, quality of life, management, clinical outcomes, and comorbidities associated with VLP were analyzed. Twenty-four patients were identified with a mean (standard deviation [SD]) follow-up time of 19.3 (13.8) months. Classical VLP with glazed erythema was found in seven (29.2%) patients, erosive VLP was present in 15 (62.5%) patients, and hypertrophic VLP in two (8.3%). Seven patients had additional cutaneous involvement, while six patients had both vulval and oral mucosal involvement. The labia minora was the most frequently affected anatomical site (83.3%), followed by the clitoris (58.3%). Scarring lesions were found in 62.5% (n = 15) of patients. All study participants received treatment with potent and/or superpotent topical corticosteroids but 50% required systemic therapy (acitretin, corticosteroids, or hydroxychloroquine). Five (20.8%) patients underwent surgery due to adhesions and scarring resulting from VLP. One patient was diagnosed with a vulval squamous cell carcinoma during long-term follow-up. The mean (SD) Dermatology Life Quality Index score was 8.4 (5.5) at presentation and 8.9 (6.8) at the end of follow-up. In conclusion, VLP was associated with moderate quality of life impairments which persisted despite treatment, suggesting that current treatments for VLP are inadequate.

Differentially Regulated miRNAs and Their Related Molecular Pathways in Lichen Sclerosus
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Cells . 2021 Sep 2;10(9):2291. doi: 10.3390/cells10092291.
https://pubmed.ncbi.nlm.nih.gov/34571940/

Lichen sclerosus (LS) is a chronic inflammatory skin disorder with unknown pathogenesis. The aberrant expression of microRNAs (miRNAs) is considered to exert a crucial role in LS. We used the next-generation sequencing technology (RNASeq) for miRNA profiling and Ingenuity Pathway Analysis (IPA) for molecular network analysis. We performed qRT-PCR, miRNA transfection and Matrigel assays for functional studies. We identified a total of 170 differentially expressed miRNAs between female LS and matched adjacent normal tissue using RNASeq, with 119 upregulated and 51 downregulated. Bioinformatics analysis revealed molecular networks that may shed light on the pathogenesis of LS. We verified the expression of a set of miRNAs that are related to autoimmunity, such as upregulated miR-326, miR-142-5p, miR-155 and downregulated miR-664a-3p and miR-181a-3p in LS tissue compared to the matched adjacent normal tissue. The differentially expressed miRNAs were also verified in blood samples from LS patients compared to healthy female volunteers. Functional studies demonstrated that a forced expression of miR-142-5p in human dermal fibroblast PCS-201-010 cells resulted in decreased cell proliferation and migration. These findings suggest that differentially expressed miRNAs may play an important role in LS pathogenesis; therefore, they could serve as biomarkers for LS management.

Risk of vulvar squamous cell carcinoma in lichen sclerosus and lichen planus: a systematic review
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J Obstet Gynaecol Can . 2021 Oct 19;S1701-2163(21)00763-5. doi: 10.1016/j.jogc.2021.09.023.
https://pubmed.ncbi.nlm.nih.gov/34678521/

Objectives: The objectives of this study were to determine: 1) the prevalence of lichen sclerosus (LS) and lichen planus (LP) present in association with vulvar squamous cell carcinoma (VSCC), and 2) the incidence and absolute risk of developing VSCC in LS and LP. **Methods:** A search was performed of MEDLINE, EMBASE and CINAHL databases. Three independent reviewers screened articles published before September 1, 2020, first on title/abstract and then on the full text. Women with a history of VSCC, human papillomavirus, smoking, or autoimmune disease were excluded. Newcastle-Ottawa observational study scales were used to assess the risk of bias and methodological quality of the included studies. Of the 3132 studies assessed, 31 were selected for analysis. Due to study heterogeneity, a qualitative synthesis was conducted. **Results:** The prevalence of LS and LP in association with VSCC ranged from 0% (95% CI 0-5) to 83% (95% CI 36-100) and 1% (95% CI 0-7) to 33% (95% CI 4-78), respectively. The incidence of VSCC ranged from 1.16 (95% CI 0.03-6.44) to 13.67 (95% CI 5.50-28.17) per 1000 person-years for LS. The absolute risk of developing VSCC in patients ranged from 0.0% (95% CI 0.0-5.52) to 21.88% (95% CI 9.28-39.97) with LS and was 1.16% (95% CI 0.1-4.1) with LP. Incidence was not calculable for LP owing to study characteristics. **Conclusions:** This review provides evidence that there is an increased risk of developing VSCC in women with LS, while associations with LP are less clear. Early identification, treatment, and long-term follow-up are essential to prevent potential malignant progression of these vulvar dermatoses.

The "CIV Classification," a New Proposal for the Architectural Grading of Vulvar Lichen Sclerosus

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J Low Genit Tract Dis . 2021 Oct 1;25(4):291-295. doi: 10.1097/LGT.0000000000000627.
https://pubmed.ncbi.nlm.nih.gov/34542084/

Objectives: The purpose of this cross-sectional study was to prepare a reliable and easy-to-use architectural classification for vulvar lichen sclerosus (VLS) aimed at defining the morphological patterns of this condition. **Materials and methods:** An expert panel composed by 7 physicians with expertise in clinical care of vulvar conditions outlined the architectural criteria for the definition of VLS severity (phimosis of the clitoris, involvement of the interlabial sulci, narrowing of the vulvar introitus), identifying 5 grades to build up a classification. Thirteen physicians with 2-30 years expertise in vulvar diseases (nonexpert group) were asked to evaluate 3-5 pictures from 137 patients. Each physician individually assigned a grade to each case, according to the previously mentioned criteria. Interrater reliability was analyzed by means of intraclass correlation coefficient (ICC). The reliability concerning the 2 classifications of each rater was analyzed by means of κ statistic. Intraobserver and interobserver reliability in vivo was analyzed by means of κ index. **Results:** This study provides a new classification of VLS, based on defined anatomical criteria and graded into mutually exclusive progressive classes.The ICC analysis showed a substantial interrater reliability of the classification, ICC = 0.89 (0.87-0.91), both in the expert panel and in the nonexpert group (ICC = 0.92 and 0.87, respectively). An "almost perfect" intraobserver and interobserver reliability was achieved among physicians in vivo (κ = 0.93). **Conclusions:** Our classification showed a high reliability. It is easy to use, and it can be applied in clinical practice and eventually, in the evaluation of regenerative and cosmetic surgery.

NASPAG Clinical Opinion: Diagnosis and Management of Lichen Sclerosus in the Pediatric and Adolescent Patient

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J Pediatr Adolesc Gynecol . 2021 Oct 2;S1083-3188(21)00296-5. doi: 10.1016/j.jpag.2021.09.008.
https://pubmed.ncbi.nlm.nih.gov/34610442/

This Clinical Opinion replaces the NASPAG Clinical Recommendation: Pediatric Lichen Sclerosus published in 2014. The objective of this document is to provide guidance in the diagnosis and management of vulvar lichen sclerosus (LS) in the pediatric and adolescent patient in order to treat patient symptoms and reduce long-term sequelae. LS is a chronic inflammatory condition affecting the anogenital region that may present in the prepubertal or adolescent patient. Clinical presentations include significant pruritus, loss of pigmentation and vulvar adhesions with loss of normal vulvar architecture. Management includes topical agents for induction and maintenance therapy, as well as long-term follow-up for identification and treatment of recurrence and sequelae. This document is intended for use by both primary and specialty pediatric and adolescent gynecology (PAG) providers, including specialists in pediatrics, gynecology, adolescent medicine, and dermatology.

Vulvar vitiligo and lichen sclerosus in children: A clinical challenge

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Pediatr Dermatol . 2021 Sep;38(5):1012-1019. doi: 10.1111/pde.14771. Epub 2021 Sep 24.
https://pubmed.ncbi.nlm.nih.gov/34561885/

Vulvar vitiligo (VV) and vulvar lichen sclerosus (VLS), both feature skin and mucosal hypo-/depigmentation. The aim of this study was to describe the clinical and dermoscopic features of VV and VLS in the pediatric population, providing diagnostic clues, and to define their association. We performed a systematic literature review of the clinical and dermoscopic features of pediatric VV and VLS. An observational study was conducted on children affected by VLS associated with VV, referred to the Dermatology Unit of the Sant'Orsola Polyclinic in Bologna, Italy. Medical history, age at diagnosis, ethnicity, clinical and dermoscopic features, and symptoms were recorded for all patients. 124 cases of VLS and 10 cases of VV were reviewed. Clinical manifestations included hypo-/depigmented patches in both conditions, while ecchymosis/purpura and fissures/erosion were observed in VLS. Symptoms including pruritus, pain, or burning were reported only by VLS patients. In our study five patients with VLS associated with VV were retrieved. Clinical features included well-demarcated depigmented patches in VV and translucent areas, erythema, ecchymoses/purpura, and labial fusion in VLS. Dermoscopy showed white structureless areas with a whipped cream-like appearance, linear or dotted vessels, white chrysalis-like structures, erosion and red-purpuric blotches in VLS and reduced pigment network or pigment absence, intralesional spots of residual pigmentation and telangiectasias in VV. Symptoms were present in all patients. Both VV and VLS show hypo-/depigmented patches. In the presence of associated symptoms, possible VLS should be investigated with clinical and dermoscopic examination to achieve a prompt diagnosis.

Recognition and diagnosis of vulvar dermatoses
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Case Rep Womens Health. 2021 Jul 24;32:e00344. doi:10.1016/j.crwh.2021.e00344. eCollection 2021 Oct.
https://pubmed.ncbi.nlm.nih.gov/34386354/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8342896/

Diagnosing late-stage vulvar lichen sclerosus (VLS) is rarely difficult. If patients present with hallmark white depigmentation, texture change, and vulvar scarring we can focus the clinical visit on education and treatment options. However, patients should not have to wait for architectural obliteration to receive a diagnosis. Treating patients with early, undifferentiated disease can be a humbling experience.

Nonablative radiofrequency in the treatment of refractory vulvar lichen sclerosus: A case series
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JAAD Case Rep . 2021 Oct 1;17:122-125. doi: 10.1016/j.jdcr.2021.09.028. eCollection 2021 Nov.
https://pubmed.ncbi.nlm.nih.gov/34754892/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8556751/

Vulvar lichen sclerosus (VLS) is a chronic lymphocyte-mediated inflammatory dermatosis that mainly affects postmenopausal women. It affects both the dermis and the epidermis and is characterized by the symptom of vulvar pruritus and the presence of pearly white plaques, which can group together and progressively assume a parched and wrinkled skin appearance. The etiology of VLS is still unknown; however, there is evidence of a multifactorial basis. The standard treatment is high-potency topical steroid ointment; however, in addition to presenting various side effects and not curing the disease, this treatment is not always effective. Patients who do not respond to this treatment have VLS that is considered refractory to therapeutic options, making the investigation and experimentation of new therapies important. Nonablative radiofrequency (NARF), due to its controlled thermal effect, promotes vasodilation, increased circulation, an increase in defense cells, greater cellular nutrition, and hydration. The histopathologic results found with the use of NARF in dermatology and in the treatment of genitourinary syndrome of menopause suggest the applicability of this method. The clinical cases described in this article are of women with VLS who had already undergone other treatments without success and responded to the use of NARF, and in whom histologic or vulvoscopic developments were registered through imaging. Symptoms were classified using a visual pain scale, colored and adapted, graduated from 0 to 10, forming part of questionnaires applied before and after treatment. The protocol used in these cases included the application of 3 sessions of NARF, each of 15 minutes at a temperature of 41°C, with a monthly interval between them.

Childhood vulvar mucous membrane pemphigoid
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J Pediatr Adolesc Gynecol . 2021 Nov 2;S1083-3188(21)00329-6. doi: 10.1016/j.jpag.2021.10.010.
https://pubmed.ncbi.nlm.nih.gov/34740758/

Background: Autoimmune bullous diseases in childhood are a diagnostic challenge. **Case:** We present the case of an 11-year-old girl with recurrent vulvar erosions since early childhood. She had been referred to a child abuse unit under the suspicion of sexual abuse. She responded well to dapsone and

topical corticosteroids. **Summary and conclusion:** Our review focuses on previously reported cases of pemphigoid (bullous or mucous membrane) in childhood with exclusively genital involvement as well as summarizes mucous membrane pemphigoid cases diagnosed during childhood. There seems to be a differentiated form of pemphigoid predominantly affecting girls with exclusively vulvar involvement and with good prognosis. Dermatologic evaluation and a skin biopsy with direct immunofluorescence are key to diagnosing a mucous membrane pemphigoid. Further antigenic studies are needed to nosologically classify the disease properly.

Dermatographism with vulvar symptoms

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Int J Womens Dermatol. 2021 May 5;7(4):454-457. doi: 10.1016/j.ijwd.2021.04.008. eCollection 2021 Sep.
https://pubmed.ncbi.nlm.nih.gov/34621958/

Dermatographism (DG) is characterized by a localized, inducible, wheal-and-flare response along the distribution of mechanical pressure. We report an illustrative case of DG with vulvar symptoms (DG-VS) and review the literature on this rarely recognized but easily treated etiology of vulvar complaints. A 35-year-old woman presented with a 1-year history of vulvar pruritus unresponsive to antifungal, antibacterial, and steroid treatments. A prior punch biopsy was nondiagnostic. Vulvar examination revealed normal architecture and no cutaneous abnormalities. She was markedly dermatographic with a scratch test. DG-VS was diagnosed. The patient achieved complete symptomatic control on low-dose hydroxyzine. She maintains excellent control at 3.5 years. In the literature, a typical patient with DG-VS is of reproductive age, with several years' history of vulvar symptoms (itching, burning, pain, or swelling) and repeated empiric treatment for infectious/inflammatory etiologies. Exacerbation with sexual activity, menstruation, or wearing tight clothing is characteristic and supports the role of mechanical pressure in inducing focal symptoms. Dermatologic changes to the vulvar skin are rarely noted. DG-VS is diagnosed based on clinical findings, symptom patterns, and a positive scratch test and is treated with antihistamines. DG-VS remains absent from current vulvar disease guidelines. In the complex world of vulvar pain and itch, an etiology so easily screened for and readily treated warrants consideration.